```
          10         20         30         40         50         60         70
           *          *          *          *          *          *          *
           *          *          *          *          *          *          *
      GACGGATCGG GAGATCTCCC GATCCCCTAT GGTCGACTCT CAGTACAATC TGCTCTGATG CCGCATAGTT

          80         90        100        110        120        130        140
           *          *          *          *          *          *          *
           *          *          *          *          *          *          *
      AAGCCAGTAT CTGCTCCCTG CTTGTGTGTT GGAGGTCGCT GAGTAGTGCG CGAGCAAAAT TTAAGCTACA

         150        160        170        180        190        200        210
           *          *          *          *          *          *          *
           *          *          *          *          *          *          *
      ACAAGGCAAG GCTTGACCGA CAATTGCATG AAGAATCTGC TTAGGGTTAG GCGTTTTGCG CTGCTTCGCG

         220        230        240        250        260        270        280
           *          *          *          *          *          *          *
           *          *          *          *          *          *          *
      ATGTACGGGC CAGATATACG CGTTGACATT GATTATTGAC TAGTTATTAA TAGTAATCAA TTACGGGGTC

         290        300        310        320        330        340        350
           *          *          *          *          *          *          *
           *          *          *          *          *          *          *
      ATTAGTTCAT AGCCCATATA TGGAGTTCCG CGTTACATAA CTTACGGTAA ATGGCCCGCC TGGCTGACCG

         360        370        380        390        400        410        420
           *          *          *          *          *          *          *
           *          *          *          *          *          *          *
      CCCAACGACC CCCGCCCATT GACGTCAATA ATGACGTATG TTCCCATAGT AACGCCAATA GGGACTTTCC

         430        440        450        460        470        480        490
           *          *          *          *          *          *          *
           *          *          *          *          *          *          *
      ATTGACGTCA ATGGGTGGAC TATTTACGGT AAACTGCCCA CTTGGCAGTA CATCAAGTGT ATCATATGCC

         500        510        520        530        540        550        560
           *          *          *          *          *          *          *
           *          *          *          *          *          *          *
      AAGTACGCCC CCTATTGACG TCAATGACGG TAAATGGCCC GCCTGGCATT ATGCCCAGTA CATGACCTTA

         570        580        590        600        610        620        630
           *          *          *          *          *          *          *
           *          *          *          *          *          *          *
      TGGGACTTTC CTACTTGGCA GTACATCTAC GTATTAGTCA TCGCTATTAC CATGGTGATG CGGTTTTGGC

         640        650        660        670        680        690        700
           *          *          *          *          *          *          *
           *          *          *          *          *          *          *
      AGTACATCAA TGGGCGTGGA TAGCGGTTTG ACTCACGGGG ATTTCCAAGT CTCCACCCCA TTGACGTCAA

         710        720        730        740        750        760        770
           *          *          *          *          *          *          *
           *          *          *          *          *          *          *
      TGGGAGTTTG TTTTGGCACC AAAATCAACG GGACTTTCCA AAATGTCGTA ACAACTCCGC CCCATTGACG

         780        790        800        810        820        830        840
           *          *          *          *          *          *          *
           *          *          *          *          *          *          *
      CAAATGGGCG GTAGGCGTGT ACGGTGGGAG GTCTATATAA GCAGAGCTCT CTGGCTAACT AGAGAACCCA

         850        860        870        880        890        900        910
           *          *          *          *          *          *          *
           *          *          *          *          *          *          *
      CTGCTTAACT GGCTTATCGA AATTAATACG ACTCACTATA GGGAGACCCA AGCTTCGCAG AATTCCTGCG

         920        930        940        950        960        970        980
           *          *          *          *          *          *          *
           *          *          *          *          *          *          *
      GCTGCTACAG TGTGTCCAGC GTCCTGCCTG GCTGTGCTGA GCGCTGGAAC AGTGGCGCAT CATTCAAGTG

         990       1000       1010       1020       1030       1040       1050
           *          *          *          *          *          *          *
           *          *          *          *          *          *          *
      CACAGTTACC CATCCTGAGT CTGGCACCTT AACTGGCACA ATTGCCAAAG TCACAGGTGA GCTCAGATGC
```

FIGURE 1

```
        1060        1070        1080        1090        1100        1110        1120
          *           *           *           *           *           *           *
ATACCAGGAC ATTGTATGAC GTTCCCTGCT CACATGCCTG CTTTCTTCCT ATAATACAGA TGCTCAACTA

        1130        1140        1150        1160        1170        1180        1190
          *           *           *           *           *           *           *
ACTGCTCATG TCCTTATATC ACAGAGGGAA ATTGGAGCTA TCTGAGGAAC TGCCCAGAAG GGAAGGGCAG

        1200        1210        1220        1230        1240        1250        1260
          *           *           *           *           *           *           *
AGGGGTCTTG CTCTCCTTGT CTGAGCCATA ACTCTTCTTT CTACCTTCCA GTGAACACCT TCCCACCCCA

        1270        1280        1290        1300        1310        1320        1330
          *           *           *           *           *           *           *
GGTCCACCTG CTACCGCCGC CGTCGGAGGA GCTGGCCCTG AATGAGCTCT TGTCCCTGAC ATGCCTGGTG

        1340        1350        1360        1370        1380        1390        1400
          *           *           *           *           *           *           *
CGAGCTTTCA ACCCTAAAGA AGTGCTGGTG CGATGGCTGC ATGGAAATGA GGAGCTGTCC CCAGAAAGCT

        1410        1420        1430        1440        1450        1460        1470
          *           *           *           *           *           *           *
ACCTAGTGTT TGAGCCCCTA AAGGAGCCAG GCGAGGGAGC CACCACCTAC CTGGTGACAA GCGTGTTGCG

        1480        1490        1500        1510        1520        1530        1540
          *           *           *           *           *           *           *
TGTATCAGCT GAAAGCTTGA TATCGAATTC CGGAGGCGGA ACCGGCAGTG CAGCCCGAAG CCCCGCAGTC

        1550        1560        1570        1580        1590
          *           *           *           *           *           *
CCCGAGCACG CGTGGCC ATG CGT CCC CTG CGC CCC CGC GCC GCG CTG CTG GCG CTC CTG
                   Met Arg Pro Leu Arg Pro Arg Ala Ala Leu Leu Ala Leu Leu>
              ___a___a___a___a___a__ORF RF[1] ___a___a___a___a___a___>

     1600       1610        1620        1630        1640        1650
        *          *           *           *           *           *           *
GCC TCG CTC CTG GCC GCG CCC CCG GTG GCC CCG GCC GAG GCC CCG CAC CTG GTG CAT
Ala Ser Leu Leu Ala Ala Pro Pro Val Ala Pro Ala Glu Ala Pro His Leu Val His>
   ___a___a___a___a___a___a___a___ORF RF[1] _a___a___a___a___a___a___a___a___>

        1660        1670        1680        1690        1700        1710
          *          .*           *           *           *           *           *
GTG GAC GCG GCC CGC GCG CTG TGG CCC CTG CGG CGC TTC TGG AGG AGC ACA GGC TTC
Val Asp Ala Ala Arg Ala Leu Trp Pro Leu Arg Arg Phe Trp Arg Ser Thr Gly Phe>
   ___a___a___a___a___a___a___a___ORF RF[1] _a___a___a___a___a___a___a___a___>

        1720        1730        1740        1750        1760        1770
          *           *           *           *           *           *           *
TGC CCC CCG CTG CCA CAC AGC CAG GCT GAC CAG TAC GTC CTC AGC TGG GAC CAG CAG
Cys Pro Pro Leu Pro His Ser Gln Ala Asp Gln Tyr Val Leu Ser Trp Asp Gln Gln>
   ___a___a___a___a___a___a___a___ORF RF[1] _a___a___a___a___a___a___a___a___>

        1780        1790        1800        1810        1820
          *           *           *           *           *           *
CTC AAC CTC GCC TAT GTG GGC GCC GTC CCT CAC CGC GGC ATC AAG CAG GTC CGG ACC
Leu Asn Leu Ala Tyr Val Gly Ala Val Pro His Arg Gly Ile Lys Gln Val Arg Thr>
   ___a___a___a___a___a___a___a___ORF RF[1] _a___a___a___a___a___a___a___a___>

     1830        1840        1850        1860        1870        1880
        *           *           *           *           *           *           *
CAC TGG CTG CTG GAG CTT GTC ACC ACC AGG GGG TCC ACT GGA CGG GGC CTG AGC TAC
His Trp Leu Leu Glu Leu Val Thr Thr Arg Gly Ser Thr Gly Arg Gly Leu Ser Tyr>
```

FIGURE 1A

```
             1890        1900        1910        1920        1930        1940
              *           *           *           *           *           *
              *     *           *     *           *     *           *     *
AAC TTC ACC CAC CTG GAC GGG TAC CTG GAC CTT CTC AGG GAG AAC CAG CTC CTC CCA
Asn Phe Thr His Leu Asp Gly Tyr Leu Asp Leu Leu Arg Glu Asn Gln Leu Leu Pro>
          ___a___a___a___a___a___a___a___ORF RF[1] _a___a___a___a___a___a___a___a___>

             1950        1960        1970        1980        1990
              *           *           *           *           *
          *     *     *     *     *     *     *     *     *     *     *
GGG TTT GAG CTG ATG GGC AGC GCC TCG GGC CAC TTC ACT GAC TTT GAG GAC AAG CAG
Gly Phe Glu Leu Met Gly Ser Ala Ser Gly His Phe Thr Asp Phe Glu Asp Lys Gln>
          _a___a___a___a___a___a___a___ORF RF[1] _a___a___a___a___a___a___a___a___>

2000        2010        2020        2030        2040        2050
 *           *           *           *           *           *
  *     *     *     *     *     *     *     *     *     *     *     *
CAG GTG TTT GAG TGG AAG GAC TTG GTC TCC AGC CTG GCC AGG AGA TAC ATC GGT AGG
Gln Val Phe Glu Trp Lys Asp Leu Val Ser Ser Leu Ala Arg Arg Tyr Ile Gly Arg>
          ___a___a___a___a___a___a___a___ORF RF[1] _a___a___a___a___a___a___a___a___>

             2060        2070        2080        2090        2100        2110
              *           *           *           *           *           *
          *     *     *     *     *     *     *     *     *     *     *
TAC GGA CTG GCG CAT GTT TCC AAG TGG AAC TTC GAG ACG TGG AAT GAG CCA GAC CAC
Tyr Gly Leu Ala His Val Ser Lys Trp Asn Phe Glu Thr Trp Asn Glu Pro Asp His>
          __a___a___a___a___a___a___a___ORF RF[1] _a___a___a___a___a___a__a___a___>

             2120        2130        2140        2150        2160
              *           *           *           *           *
          *     *     *     *     *     *     *     *     *     *     *
CAC GAC TTT GAC AAC GTC TCC ATG ACC ATG CAA GGC TTC CTG AAC TAC TAC GAT GCC
His Asp Phe Asp Asn Val Ser Met Thr Met Gln Gly Phe Leu Asn Tyr Tyr Asp Ala>
          __a___a___a___a___a___a___a___ORF RF[1] _a___a___a___a___a___a___a___a___>

2170        2180        2190        2200        2210        2220
 *           *           *           *           *           *
  *     *     *     *     *     *     *     *     *     *     *     *
TGC TCG GAG GGT CTG CGC GCC GCC AGC CCC GCC CTG CGG CTG GGA GGC CCC GGC GAC
Cys Ser Glu Gly Leu Arg Ala Ala Ser Pro Ala Leu Arg Leu Gly Gly Pro Gly Asp>
          __a___a___a___a___a___a___a___ORF RF[1] _a___a___a___a___a___a___a___a___>

   2230        2240        2250        2260        2270        2280
    *           *           *           *           *           *
     *     *     *     *     *     *     *     *     *     *     *     *
TCC TTC CAC ACC CCA CCG CGA TCC CCG CTG AGC TGG GGC CTC CTG CGC CAC TGC CAC
Ser Phe His Thr Pro Pro Arg Ser Pro Leu Ser Trp Gly Leu Leu Arg His Cys His>
          __a___a___a___a___a___a___a___ORF RF[1] _a___a___a___a___a___a___a___a___>

   2290        2300        2310        2320        2330        2340
    *           *           *           *           *           *
     *     *     *     *     *     *     *     *     *     *     *     *
GAC GGT ACC AAC TTC TTC ACT GGG GAG GCG GGC GTG CGG CTG GAC TAC ATC TCC CTC
Asp Gly Thr Asn Phe Phe Thr Gly Glu Ala Gly Val Arg Leu Asp Tyr Ile Ser Leu>
          __a___a___a___a___a___a___a___ORF RF[1] _a___a___a___a___a___a___a___a___>

      2350        2360        2370        2380        2390
       *           *           *           *           *
        *     *     *     *     *     *     *     *     *     *     *
CAC AGG AAG GGT GCG CGC AGC TCC ATC TCC ATC CTG GAG CAG GAG AAG GTC GTC GCG
His Arg Lys Gly Ala Arg Ser Ser Ile Ser Ile Leu Glu Gln Glu Lys Val Val Ala>
          __a___a___a___a___a___a___a___ORF RF[1] _a___a___a___a___a___a___a___a___>

   2400        2410        2420        2430        2440        2450
    *           *           *           *           *           *
     *     *     *     *     *     *     *     *     *     *     *     *
CAG CAG ATC CGG CAG CTC TTC CCC AAG TTC GCG GAC ACC CCC ATT TAC AAC GAC GAG
Gln Gln Ile Arg Gln Leu Phe Pro Lys Phe Ala Asp Thr Pro Ile Tyr Asn Asp Glu>
          __a___a___a___a___a___a___a___ORF RF[1] _a___a___a___a___a___a___a___a___>
```

FIGURE 1B

```
         2460              2470              2480              2490              2500              2510
  *         *        *         *        *         *        *         *        *         *        *
GCG GAC CCG CTG GTG GGC TGG TCC CTG CCA CAG CCG TGG AGG GCG GAC GTG ACC TAC
Ala Asp Pro Leu Val Gly Trp Ser Leu Pro Gln Pro Trp Arg Ala Asp Val Thr Tyr>
___a___a___a___a___a___a___a____ORF RF[1] _a___a___a___a___a___a___a___a___>

                   2520              2530              2540              2550              2560
     *         *        *         *        *         *        *         *        *         *
GCG GCC ATG GTG GTG AAG GTC ATC GCG CAG CAT CAG AAC CTG CTA CTG GCC AAC ACC
Ala Ala Met Val Val Lys Val Ile Ala Gln His Gln Asn Leu Leu Leu Ala Asn Thr>
___a___a___a___a___a___a___a____ORF RF[1] _a___a___a___a___a___a___a___a___>

   2570              2580              2590              2600              2610              2620
     *         *        *         *        *         *        *         *        *         *
ACC TCC GCC TTC CCC TAC GCG CTC CTG AGC AAC GAC AAT GCC TTC CTG AGC TAC CAC
Thr Ser Ala Phe Pro Tyr Ala Leu Leu Ser Asn Asp Asn Ala Phe Leu Ser Tyr His>
   ___a___a___a___a___a___a___a____ORF RF[1] _a___a___a___a___a___a___a___a___>

      2630              2640              2650              2660              2670              2680
        *         *        *         *        *         *        *         *        *         *
CCG CAC CCC TTC GCG CAG CGC ACG CTC ACC GCG CGC TTC CAG GTC AAC AAC ACC CGC
Pro His Pro Phe Ala Gln Arg Thr Leu Thr Ala Arg Phe Gln Val Asn Asn Thr Arg>
   ___a___a___a___a___a___a___a____ORF RF[1] _a___a___a___a___a___a___a___a___>

           2690              2700              2710              2720              2730
        *         *        *         *        *         *        *         *        *
CCG CCG CAC GTG CAG CTG TTG CGC AAG CCG GTG CTC ACG GCC ATG GGG CTG CTG GCG
Pro Pro His Val Gln Leu Leu Arg Lys Pro Val Leu Thr Ala Met Gly Leu Leu Ala>
   ___a___a___a___a___a___a___a____ORF RF[1] _a___a___a___a___a___a___a___a___>

                   2750              2760              2770              2780              2790
   2740    *        *         *        *         *        *         *        *        *
CTG CTG GAT GAG GAG CAG CTC TGG GCC GAA GTG TCG CAG GCC GGG ACC GTC CTG GAC
Leu Leu Asp Glu Glu Gln Leu Trp Ala Glu Val Ser Gln Ala Gly Thr Val Leu Asp>
   ___a___a___a___a___a___a___a____ORF RF[1] _a___a___a___a___a___a___a___a___>

                                              2830              2840              2850
   2800              2810              2820
     *         *        *         *        *         *        *         *        *         *
AGC AAC CAC ACG GTG GGC GTC CTG GCC AGC GCC CAC CGC CCC CAG GGC CCG GCC GAC
Ser Asn His Thr Val Gly Val Leu Ala Ser Ala His Arg Pro Gln Gly Pro Ala Asp>
   ___a___a___a___a___a___a___a____ORF RF[1] _a___a___a___a___a___a___a___a___>

                                                       2890              2900              2910
      2860              2870              2880
        *         *        *         *        *         *        *         *        *         *
GCC TGG CGC GCC GCG GTG CTG ATC TAC GCG AGC GAC GAC ACC CGC GCC CAC CCC AAC
Ala Trp Arg Ala Ala Val Leu Ile Tyr Ala Ser Asp Asp Thr Arg Ala His Pro Asn>
   ___a___a___a___a___a___a___a____ORF RF[1] _a___a___a___a___a___a___a___a___>

                                              2940              2950              2960
      2920              2930
        *         *        *         *        *         *        *        *         *        *
CGC AGC GTC GCG GTG ACC CTG CGG CTG CGC GGG GTG CCC CCC GGC CCG GGC CTG GTC
Arg Ser Val Ala Val Thr Leu Arg Leu Arg Gly Val Pro Pro Gly Pro Gly Leu Val>
   ___a___a___a___a___a___a___a____ORF RF[1] _a___a___a___a___a___a___a___a___>

                                     3000              3010              3020
   2970              2980              2990
     *         *        *         *        *         *        *         *        *        *
TAC GTC ACG CGC TAC CTG GAC AAC GGG CTC TGC AGC CCC GAC GGC GAG TGG CGG CGC
Tyr Val Thr Arg Tyr Leu Asp Asn Gly Leu Cys Ser Pro Asp Gly Glu Trp Arg Arg>
   ___a___a___a___a___a___a___a____ORF RF[1] _a___a___a___a___a___a___a___a___>

         3030              3040              3050              3060              3070              3080
     *         *        *         *        *         *        *         *        *         *        *
```

FIGURE 1C

```
CTG GGC CGG CCC GTC TTC CCC ACG GCA GAG CAG TTC CGG CGC ATG CGC GCG GCT GAG
Leu Gly Arg Pro Val Phe Pro Thr Ala Glu Gln Phe Arg Arg Met Arg Ala Ala Glu>
___a___a___a___a___a___a___a____ORF RF[1] _a___a___a___a___a___a___a___a___>
        3090          3100         3110         3120         3130
         *             *            *            *            *        *
GAC CCG GTG GCC GCG GCG CCC CGC CCC TTA CCC GCC GGC GGC CGC CTG ACC CTG CGC
Asp Pro Val Ala Ala Ala Pro Arg Pro Leu Pro Ala Gly Gly Arg Leu Thr Leu Arg>
___a___a___a___a___a___a___a____ORF RF[1] _a___a___a___a___a___a___a___a___>
3140          3150         3160         3170         3180         3190
 *             *            *            *            *        *       *
CCC GCG CTG CGG CTG CCG TCG CTT TTG CTG GTG CAC GTG TGT GCG CGC CCC GAG AAG
Pro Ala Leu Arg Leu Pro Ser Leu Leu Leu Val His Val Cys Ala Arg Pro Glu Lys>
___a___a___a___a___a___a___a____ORF RF[1] _a___a___a___a___a___a___a___a___>
        3200          3210         3220         3230         3240         3250
         *             *            *            *            *        *
CCG CCC GGG CAG GTC ACG CGG CTC CGC GCC CTG CCC CTG ACC CAA GGG CAG CTG GTT
Pro Pro Gly Gln Val Thr Arg Leu Arg Ala Leu Pro Leu Thr Gln Gly Gln Leu Val>
___a___a___a___a___a___a___a____ORF RF[1] _a___a___a___a___a___a___a___a___>
          3260          3270         3280         3290         3300
           *             *            *            *            *        *
CTG GTC TGG TCG GAT GAA CAC GTG GGC TCC AAG TGC CTG TGG ACA TAC GAG ATC CAG
Leu Val Trp Ser Asp Glu His Val Gly Ser Lys Cys Leu Trp Thr Tyr Glu Ile Gln>
___a___a___a___a___a___a___a____ORF RF[1] _a___a___a___a___a___a___a___a___>
3310          3320         3330         3340         3350         3360
 *             *            *            *            *        *       *
TTC TCT CAG GAC GGT AAG GCG TAC ACC CCG GTC AGC AGG AAG CCA TCG ACC TTC AAC
Phe Ser Gln Asp Gly Lys Ala Tyr Thr Pro Val Ser Arg Lys Pro Ser Thr Phe Asn>
___a___a___a___a___a___a___a____ORF RF[1] _a___a___a___a___a___a___a___a___>
        3370          3380         3390         3400         3410         3420
         *             *            *            *            *        *
CTC TTT GTG TTC AGC CCA GAC ACA GGT GCT GTC TCT GGC TCC TAC CGA GTT CGA GCC
Leu Phe Val Phe Ser Pro Asp Thr Gly Ala Val Ser Gly Ser Tyr Arg Val Arg Ala>
___a___a___a___a___a___a___a____ORF RF[1] _a___a___a___a___a___a___a___a___>
          3430          3440         3450         3460         3470         3480
           *             *            *            *            *        *
CTG GAC TAC TGG GCC CGA CCA GGC CCC TTC TCG GAC CCT GTG CCG TAC CTG GAG GTC
Leu Asp Tyr Trp Ala Arg Pro Gly Pro Phe Ser Asp Pro Val Pro Tyr Leu Glu Val>
___a___a___a___a___a___a___a____ORF RF[1] _a___a___a___a___a___a___a___a___>
          3490          3500         3510         3520         3530         3540
           *             *            *            *            *        *
CCT GTG CCA AGA GGG CCC CCA TCC CCG GGC AAT CCA TGAG CCTGTGCTGA GCCCCAGTGG
Pro Val Pro Arg Gly Pro Pro Ser Pro Gly Asn Pro>
___a___a___a___a_ORF RF[1] ___a___a___a___a___>
        3550          3560         3570         3580         3590         3600         3610
         *             *            *            *            *        *       *
GTTGCACCTC CACCGGCAGT CAGCGAGCTG GGGCTGCACT GTGCCCATGC TGCCCTCCCA TCACCCCCTT
        3620          3630         3640         3650         3660         3670         3680
         *             *            *            *            *        *       *
TGCAATATAT TTTTATATTT TAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA AAAAAAAAAA
          3690          3700         3710         3720         3730         3740         3750
           *             *            *            *            *        *
```

FIGURE 1D

AAAAAAAAAA AAAAAAAAAG AATTCCTGCA GCCCGGGGGA TCCACTAGTT CTAGAGGGCC CGTTTAAACC

```
    3760       3770       3780       3790       3800       3810       3820
      *          *          *          *          *          *          *
CGCTGATCAG CCTCGACTGT GCCTTCTAGT TGCCAGCCAT CTGTTGTTTG CCCCTCCCCC GTGCCTTCCT

    3830       3840       3850       3860       3870       3880       3890
      *          *          *          *          *          *          *
TGACCCTGGA AGGTGCCACT CCCACTGTCC TTTCCTAATA AAATGAGGAA ATTGCATCGC ATTGTCTGAG

    3900       3910       3920       3930       3940       3950       3960
      *          *          *          *          *          *          *
TAGGTGTCAT TCTATTCTGG GGGGTGGGGT GGGGCAGGAC AGCAAGGGGG AGGATTGGGA AGACAATAGC

    3970       3980       3990       4000       4010       4020       4030
      *          *          *          *          *          *          *
AGGCATGCTG GGGATGCGGT GGGCTCTATG GCTTCTGAGG CGGAAAGAAC CAGCTGGGGC TCGAGAGCTT

    4040       4050       4060       4070       4080       4090       4100
      *          *          *          *          *          *          *
GGCGTAATCA TGGTCATAGC TGTTTCCTGT GTGAAATTGT TATCCGCTCA CAATTCCACA CAACATACGA

    4110       4120       4130       4140       4150       4160       4170
      *          *          *          *          *          *          *
GCCGGAAGCA TAAAGTGTAA AGCCTGGGGT GCCTAATGAG TGAGCTAACT CACATTAATT GCGTTGCGCT

    4180       4190       4200       4210       4220       4230       4240
      *          *          *          *          *          *          *
CACTGCCCGC TTTCCAGTCG GGAAACCTGT CGTGCCAGCT GCATTAATGA ATCGGCCAAC GCGCGGGGAG

    4250       4260       4270       4280       4290       4300       4310
      *          *          *          *          *          *          *
AGGCGGTTTG CGTATTGGGC GCTCTTCCGC TTCCTCGCTC ACTGACTCGC TGCGCTCGGT CGTTCGGCTG

    4320       4330       4340       4350       4360       4370       4380
      *          *          *          *          *          *          *
CGGCGAGCGG TATCAGCTCA CTCAAAGGCG GTAATACGGT TATCCACAGA ATCAGGGGAT AACGCAGGAA

    4390       4400       4410       4420       4430       4440       4450
      *          *          *          *          *          *          *
AGAACATGTG AGCAAAAGGC CAGCAAAAGG CCAGGAACCG TAAAAAGGCC GCGTTGCTGG CGTTTTTCCA

    4460       4470       4480       4490       4500       4510       4520
      *          *          *          *          *          *          *
TAGGCTCCGC CCCCCTGACG AGCATCACAA AAATCGACGC TCAAGTCAGA GGTGGCGAAA CCCGACAGGA

    4530       4540       4550       4560       4570       4580       4590
      *          *          *          *          *          *          *
CTATAAAGAT ACCAGGCGTT TCCCCCTGGA AGCTCCCTCG TGCGCTCTCC TGTTCCGACC CTGCCGCTTA

    4600       4610       4620       4630       4640       4650       4660
      *          *          *          *          *          *          *
CCGGATACCT GTCCGCCTTT CTCCCTTCGG GAAGCGTGGC GCTTTCTCAA TGCTCACGCT GTAGGTATCT

    4670       4680       4690       4700       4710       4720       4730
      *          *          *          *          *          *          *
CAGTTCGGTG TAGGTCGTTC GCTCCAAGCT GGGCTGTGTG CACGAACCCC CCGTTCAGCC CGACCGCTGC

    4740       4750       4760       4770       4780       4790       4800
      *          *          *          *          *          *          *
GCCTTATCCG GTAACTATCG TCTTGAGTCC AACCCGGTAA GACACGACTT ATCGCCACTG GCAGCAGCCA
```

FIGURE 1E

```
                4810        4820        4830        4840        4850        4860        4870
CTGGTAACAG GATTAGCAGA GCGAGGTATG TAGGCGGTGC TACAGAGTTC TTGAAGTGGT GGCCTAACTA

        4880        4890        4900        4910        4920        4930        4940
CGGCTACACT AGAAGGACAG TATTTGGTAT CTGCGCTCTG CTGAAGCCAG TTACCTTCGG AAAAAGAGTT

        4950        4960        4970        4980        4990        5000        5010
GGTAGCTCTT GATCCGGCAA ACAAACCACC GCTGGTAGCG GTGGTTTTTT TGTTTGCAAG CAGCAGATTA

        5020        5030        5040        5050        5060        5070        5080
CGCGCAGAAA AAAGGATCT CAAGAAGATC CTTTGATCTT TTCTACGGGG TCTGACGCTC AGTGGAACGA

        5090        5100        5110        5120        5130        5140        5150
AAACTCACGT TAAGGGATTT TGGTCATGAG ATTATCAAAA AGGATCTTCA CCTAGATCCT TTTAAATTAA

        5160        5170        5180        5190        5200        5210        5220
AAATGAAGTT TTAAATCAAT CTAAAGTATA TATGAGTAAA CTTGGTCTGA CAGTTACCAA TGCTTAATCA

        5230        5240        5250        5260        5270        5280        5290
GTGAGGCACC TATCTCAGCG ATCTGTCTAT TTCGTTCATC CATAGTTGCC TGACTCCCCG TCGTGTAGAT

        5300        5310        5320        5330        5340        5350        5360
AACTACGATA CGGGAGGGCT TACCATCTGG CCCCAGTGCT GCAATGATAC CGCGAGACCC ACGCTCACCG

        5370        5380        5390        5400        5410        5420        5430
GCTCCAGATT TATCAGCAAT AAACCAGCCA GCCGGAAGGG CCGAGCGCAG AAGTGGTCCT GCAACTTTAT

        5440        5450        5460        5470        5480        5490        5500
CCGCCTCCAT CCAGTCTATT AATTGTTGCC GGGAAGCTAG AGTAAGTAGT TCGCCAGTTA ATAGTTTGCG

        5510        5520        5530        5540        5550        5560        5570
CAACGTTGTT GCCATTGCTA CAGGCATCGT GGTGTCACGC TCGTCGTTTG GTATGGCTTC ATTCAGCTCC

        5580        5590        5600        5610        5620        5630        5640
GGTTCCCAAC GATCAAGGCG AGTTACATGA TCCCCCATGT TGTGCAAAAA AGCGGTTAGC TCCTTCGGTC

        5650        5660        5670        5680        5690        5700        5710
CTCCGATCGT TGTCAGAAGT AAGTTGGCCG CAGTGTTATC ACTCATGGTT ATGGCAGCAC TGCATAATTC

        5720        5730        5740        5750        5760        5770        5780
TCTTACTGTC ATGCCATCCG TAAGATGCTT TTCTGTGACT GGTGAGTACT CAACCAAGTC ATTCTGAGAA

        5790        5800        5810        5820        5830        5840        5850
TAGTGTATGC GGCGACCGAG TTGCTCTTGC CCGGCGTCAA TACGGGATAA TACCGCGCCA CATAGCAGAA

        5860        5870        5880        5890        5900        5910        5920
```

FIGURE 1F

CTTTAAAAGT GCTCATCATT GGAAAACGTT CTTCGGGGCG AAAACTCTCA AGGATCTTAC CGCTGTTGAG

         5930   5940   5950   5960   5970   5980   5990
            *   *   *   *   *   *   *
ATCCAGTTCG ATGTAACCCA CTCGTGCACC CAACTGATCT TCAGCATCTT TTACTTTCAC CAGCGTTTCT

         6000   6010   6020   6030   6040   6050   6060
            *   *   *   *   *   *   *
GGGTGAGCAA AAACAGGAAG GCAAAATGCC GCAAAAAAGG GAATAAGGGC GACACGGAAA TGTTGAATAC

         6070   6080   6090   6100   6110   6120   6130
            *   *   *   *   *   *   *
TCATACTCTT CCTTTTTCAA TATTATTGAA GCATTTATCA GGGTTATTGT CTCATGAGCG GATACATATT

         6140   6150   6160   6170   6180   6190   6200
            *   *   *   *   *   *   *
TGAATGTATT TAGAAAAATA AACAAATAGG GGTTCCGCGC ACATTTCCCC GAAAAGTGCC ACCTGACGTC

FIGURE 1G

FIGURE 2. SDS-POLYACRYLAMIDE GELS DEMONSTRATING IMPROVEMENTS IN PURITY

Gel using the Kakkis et al 1994, published procedure for purification

Contaminant

Iduronidase 3 ug

Contaminants
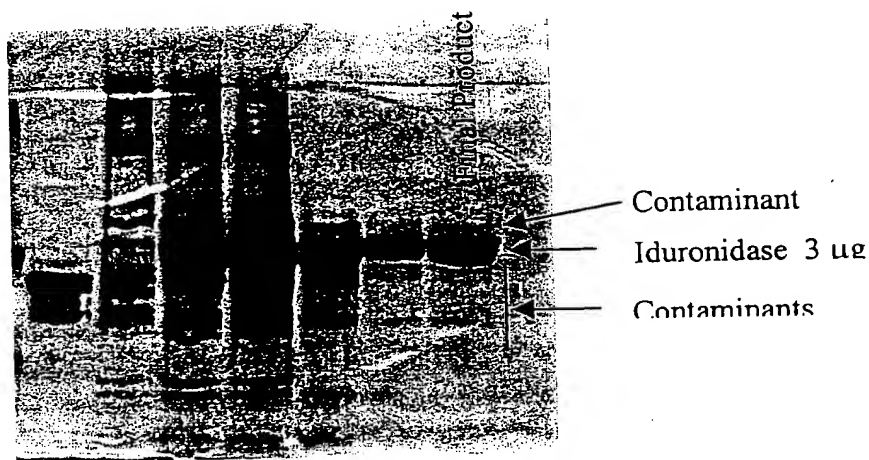
Gel using the new Galli Process contained in this application

Lane 4
Galli Process Enzyme
with few contaminants
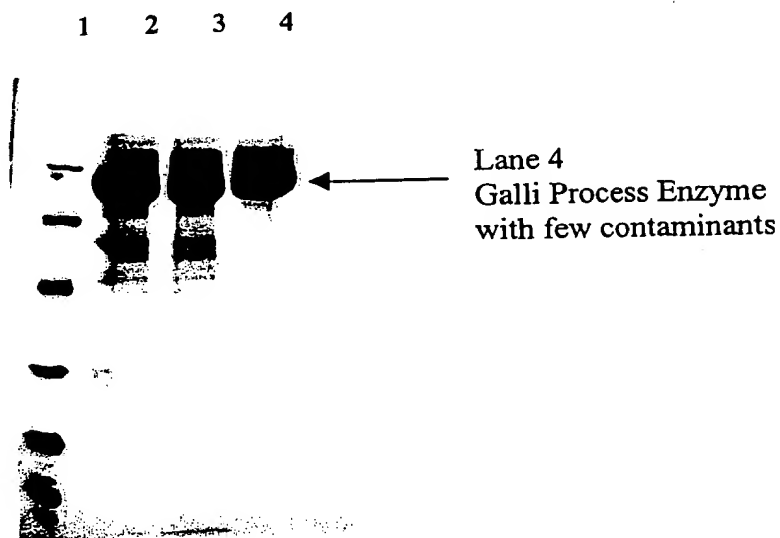
1. Molecular Weight Marker
2. Prior Process Carson (nonpublished) Batch 2000C9001 Reference Reduced (7.5 µg)
3. Same Batch 2000C9001 Reference Reduced (5.0 µg)
4. Galli Process Enzyme Batch P10006 (5.0 µg)

FIGURE 2

FIGURE 3A IDURONIDASE PRODUCTION USING THE GALLI PROCESS

Iduronidase Enzyme Activity During Production
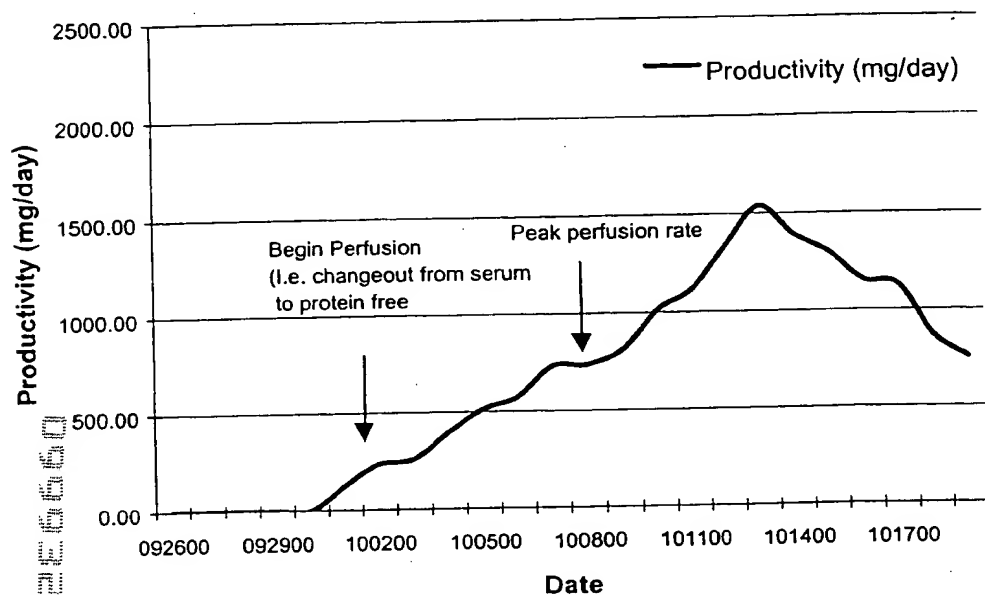
FIGURE 3B. IDURONIDASE PRODUCTION USING BUTYRATE INDUCTION

Iduronidase Production Level in Production Run PQ2
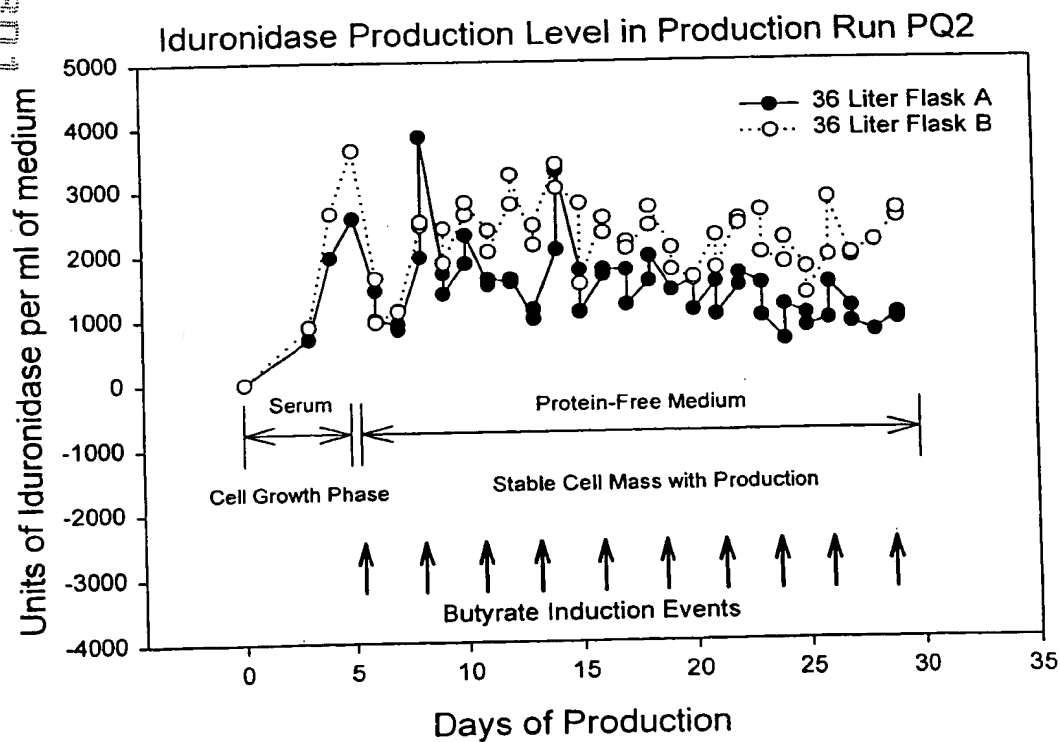
Reduction in Liver Volume During Enzyme Therapy
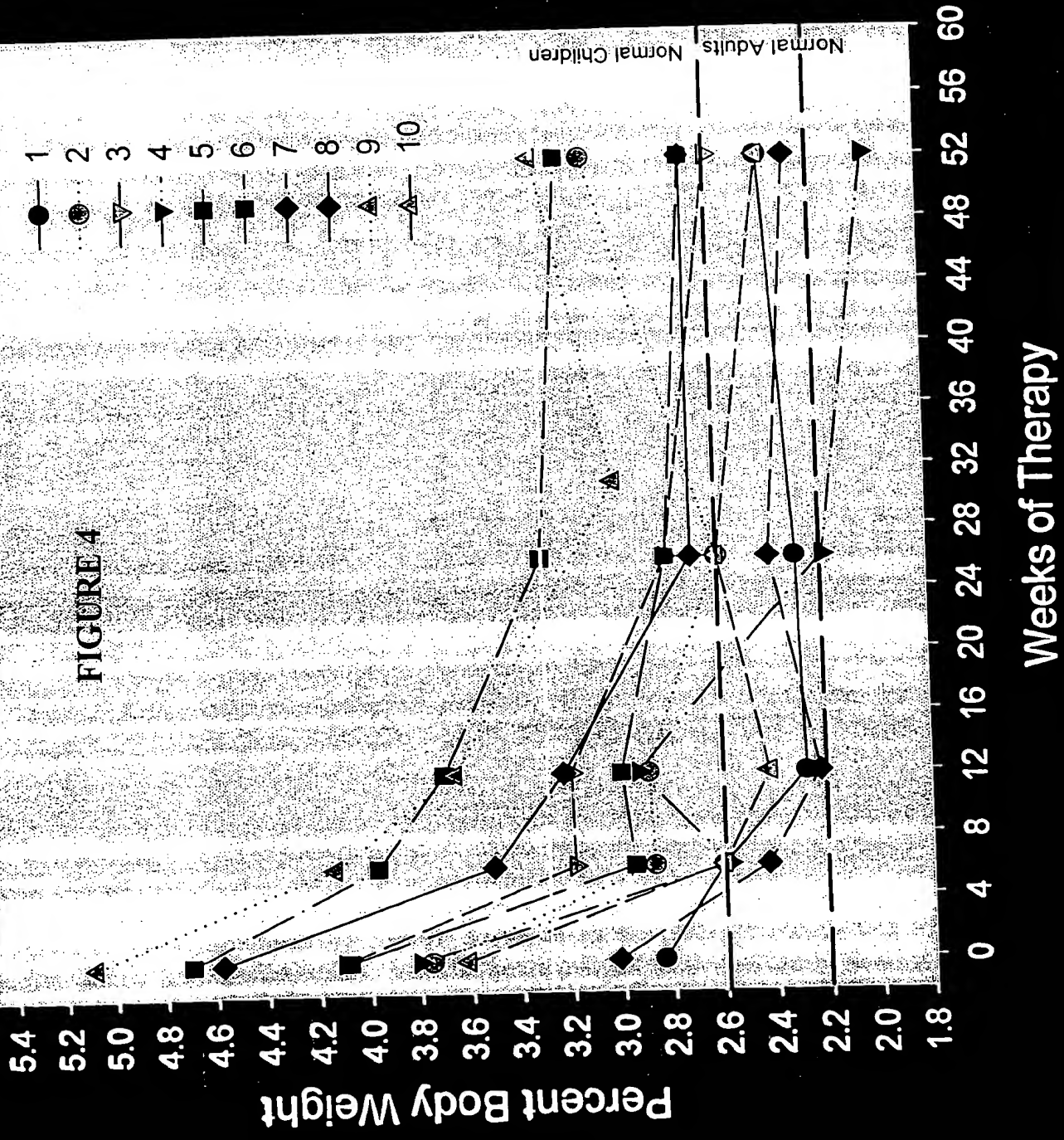
FIGURE 4

FIGURE 4

Urinary GAG Excretion During Enzyme Therapy

FIGURE 5

Percent Starting GAG vs. Weeks of Treatment

Legend: JOM001, HAC002, RCD003, SSH004, SWD005, GMD006, JAN007, NM008, CEL009, BBG010
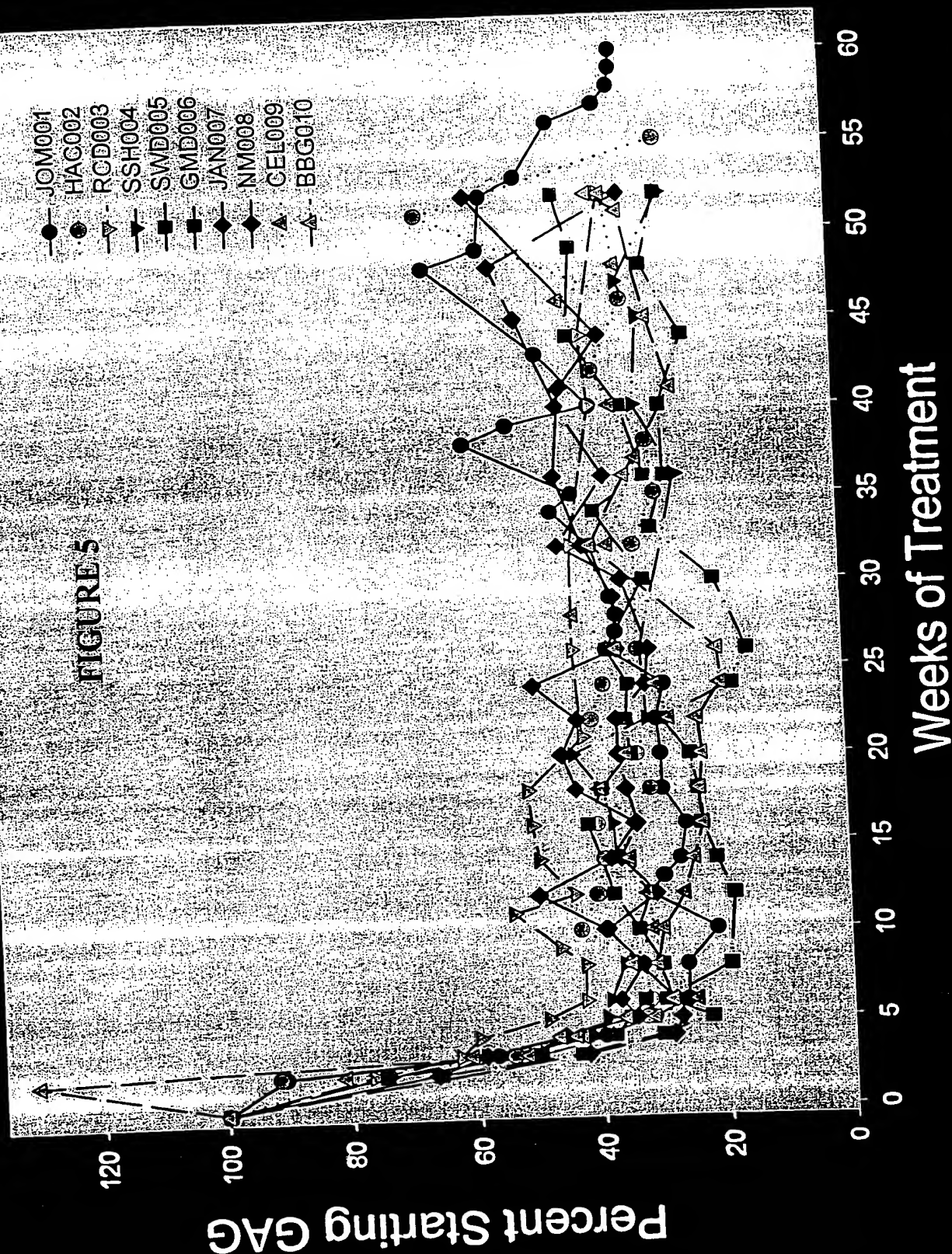
FIGURE 5

Elbow and Knee Extension in HAC002
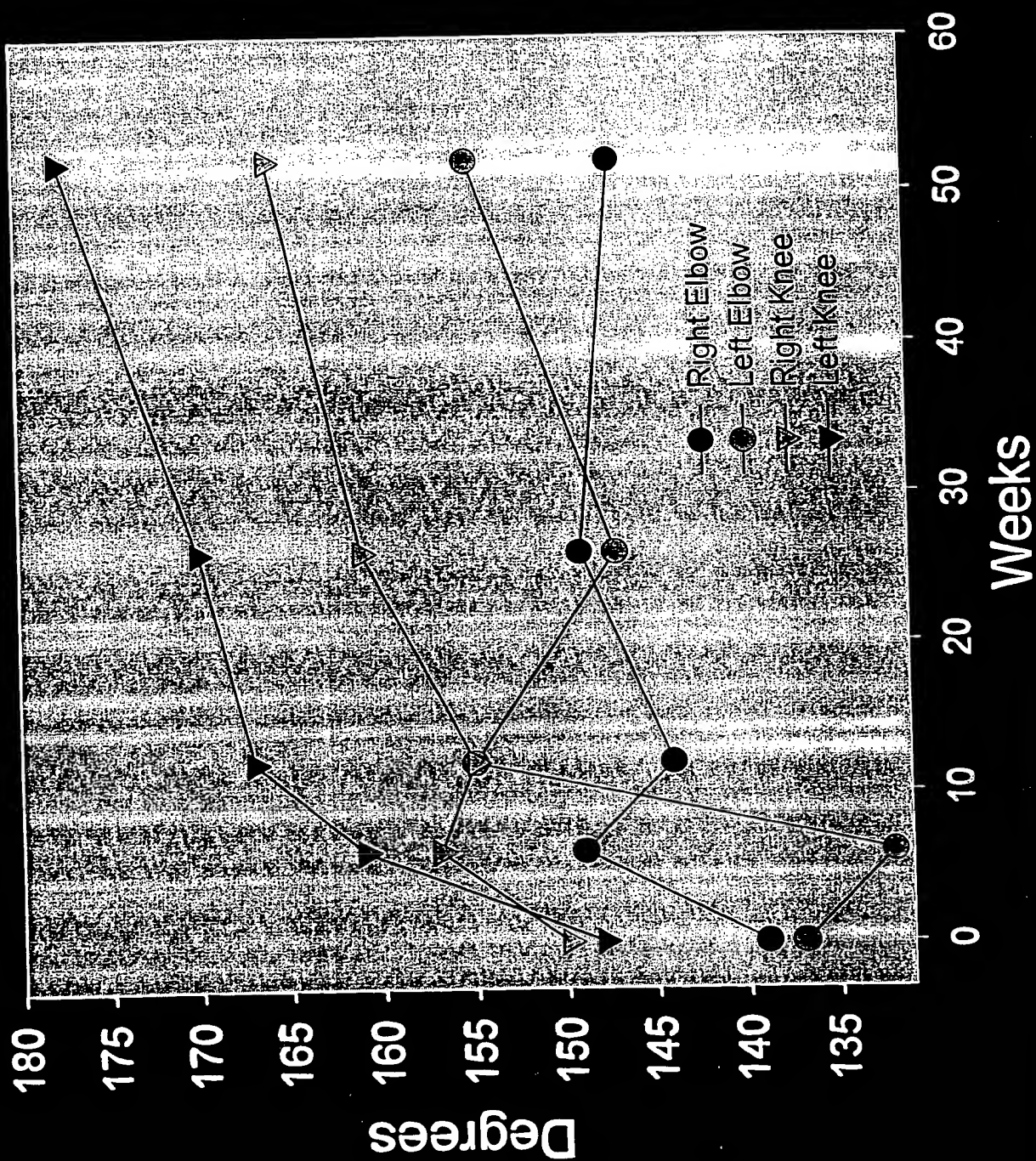
FIGURE 6

Shoulder flexion to 104 weeks
in four patients with most restriction
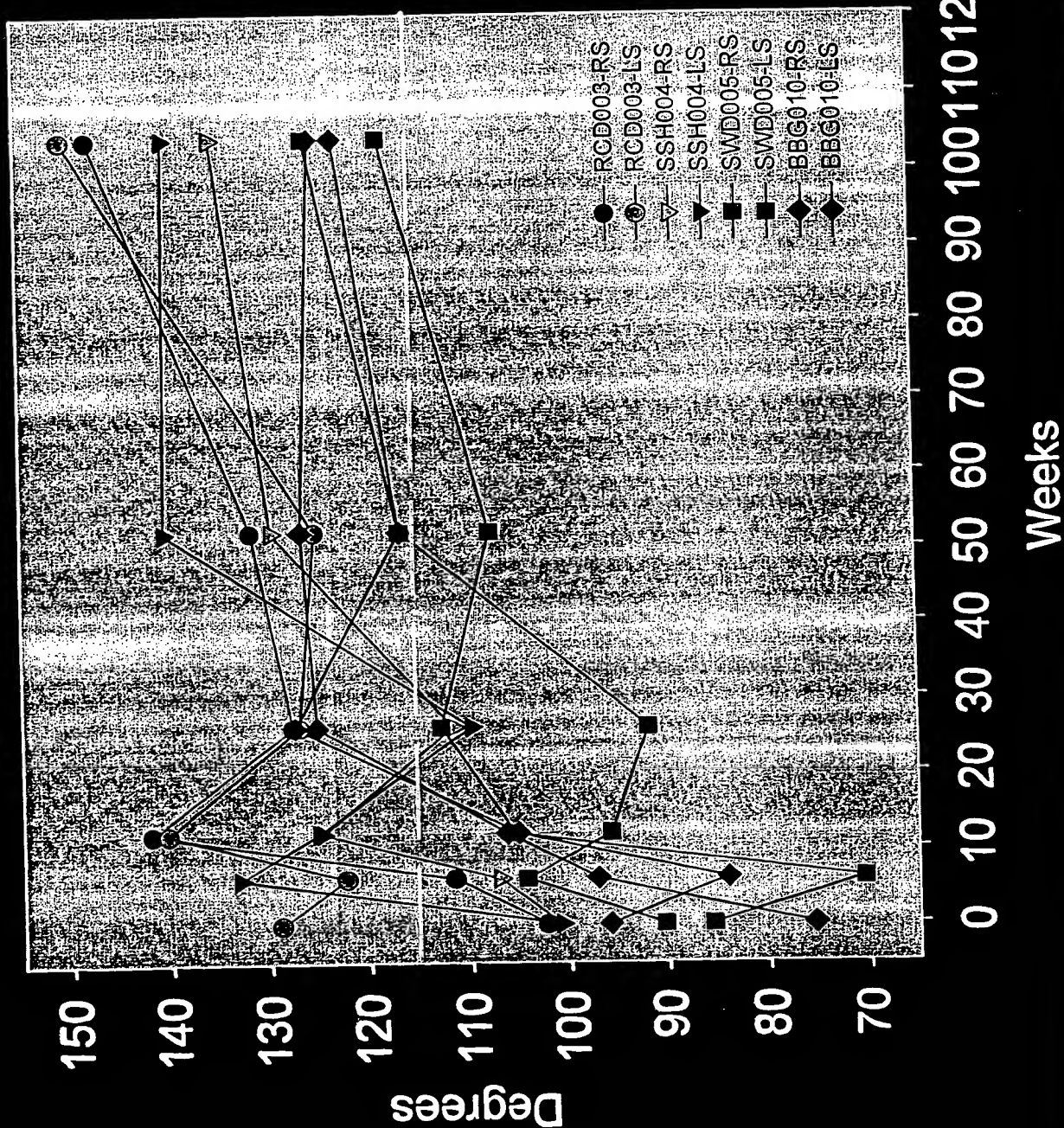
FIGURE 7

Sleep Apnea Improves
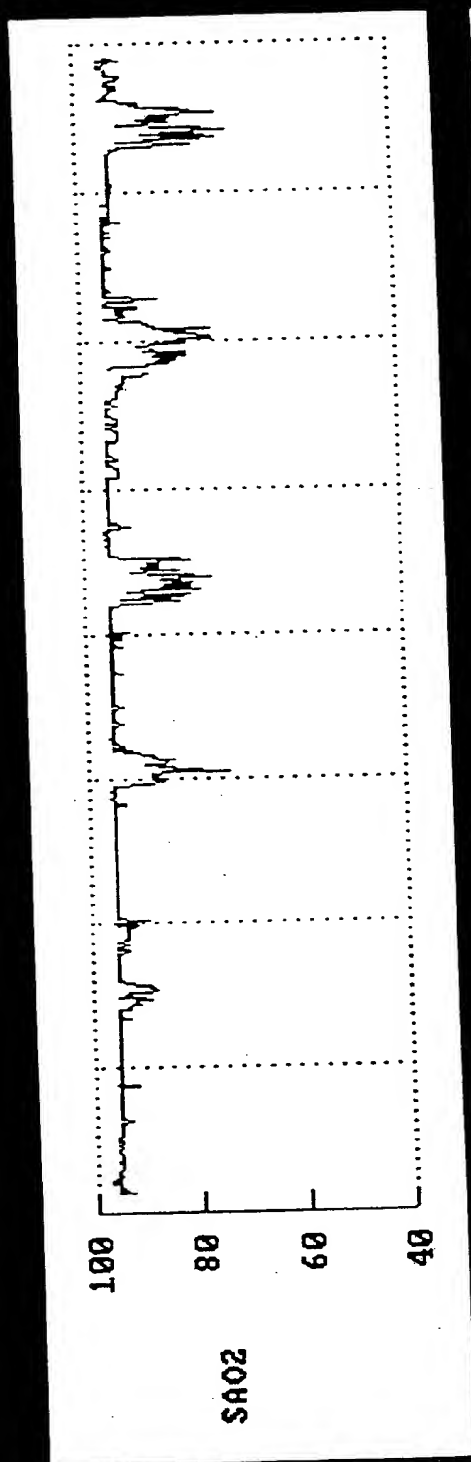
0 weeks
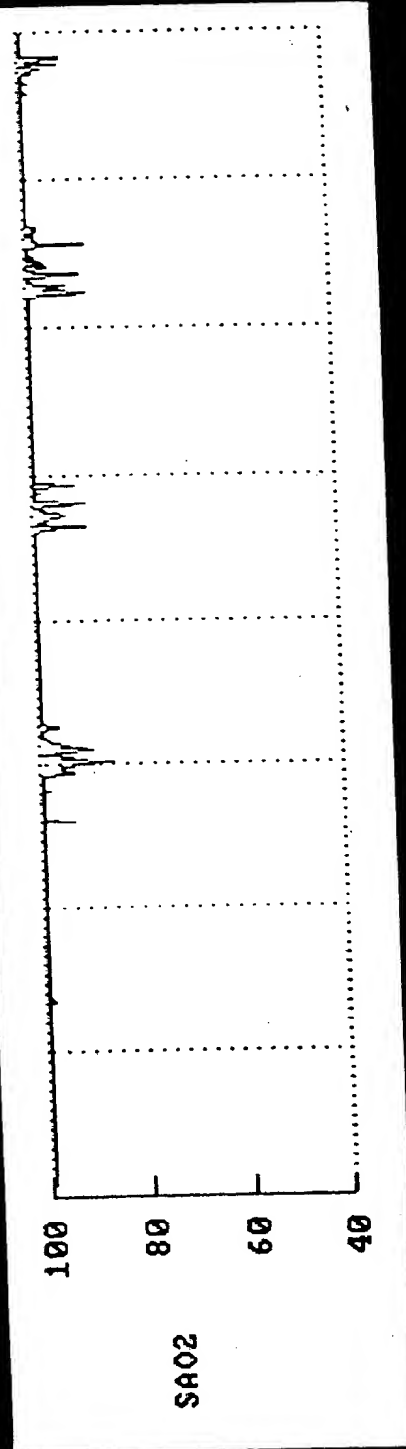
After 6 weeks

FIGURE 8

Apneas + Hypopneas During Sleep
Pre and Post Treatment

Pretreatment
26 Weeks Treatment
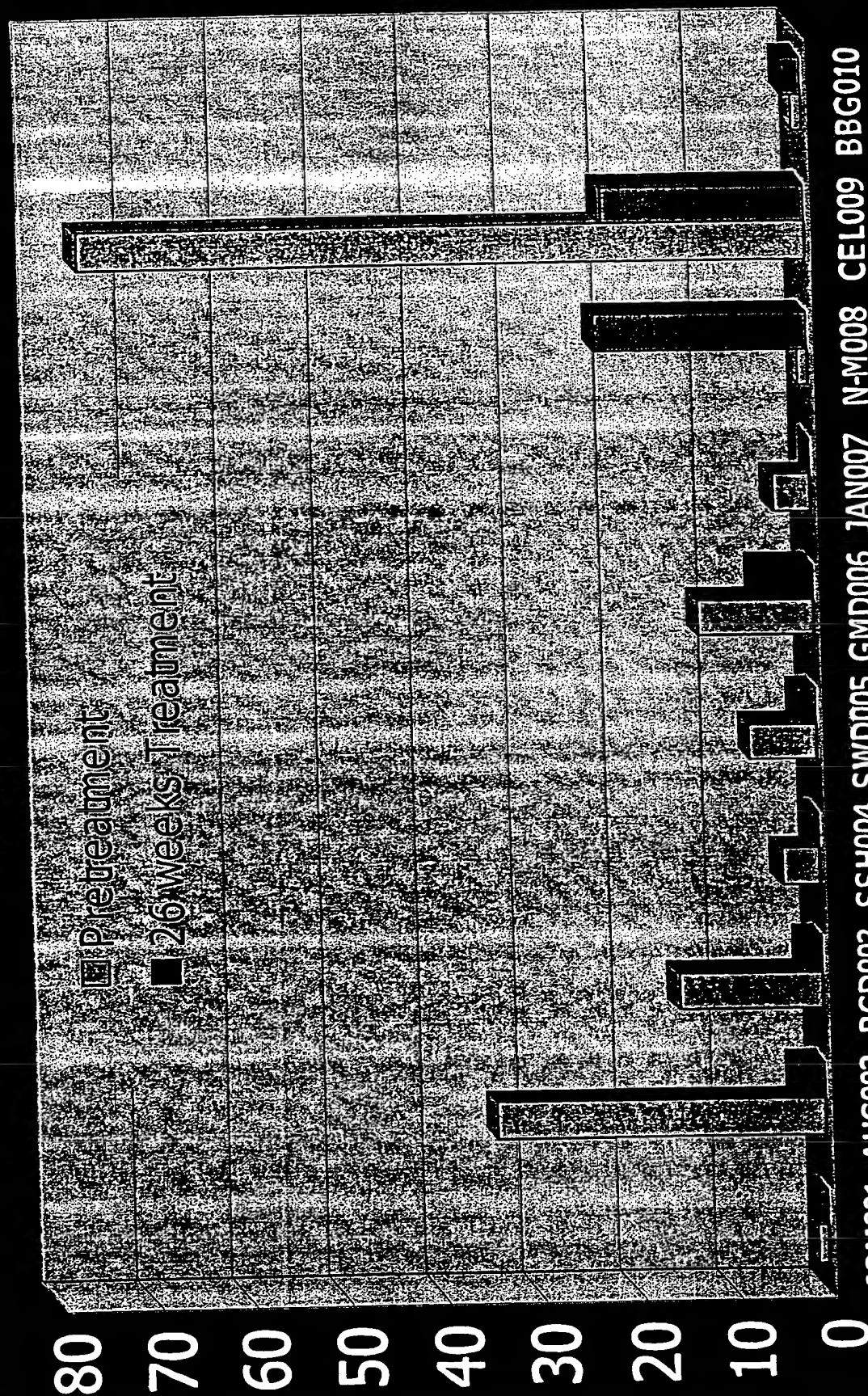
JOM001 AHC002 RCD003 SSH004 SWD005 GMD006 JAN007 N-M008 CEL009 BBG010

0 10 20 30 40 50 60 70 80

FIGURE 9

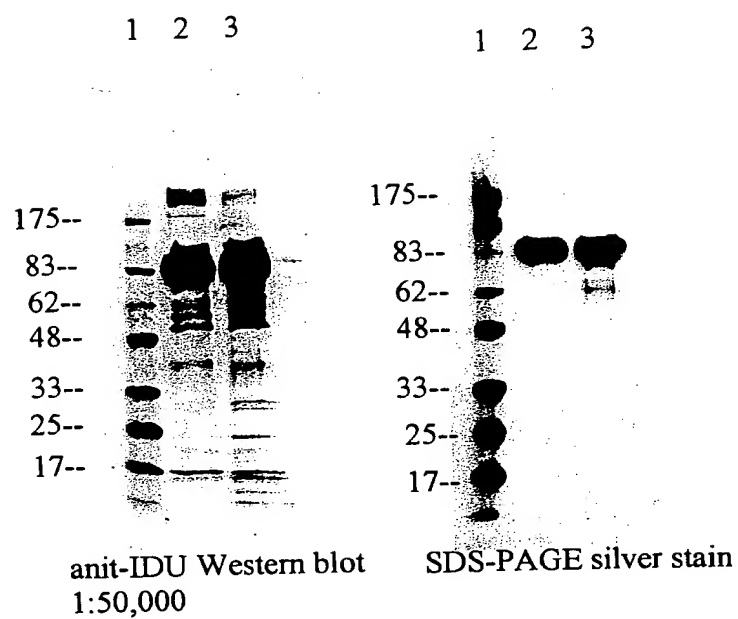Pulmonary Function Tests in GMD006

FVC   FEV1   FEV3
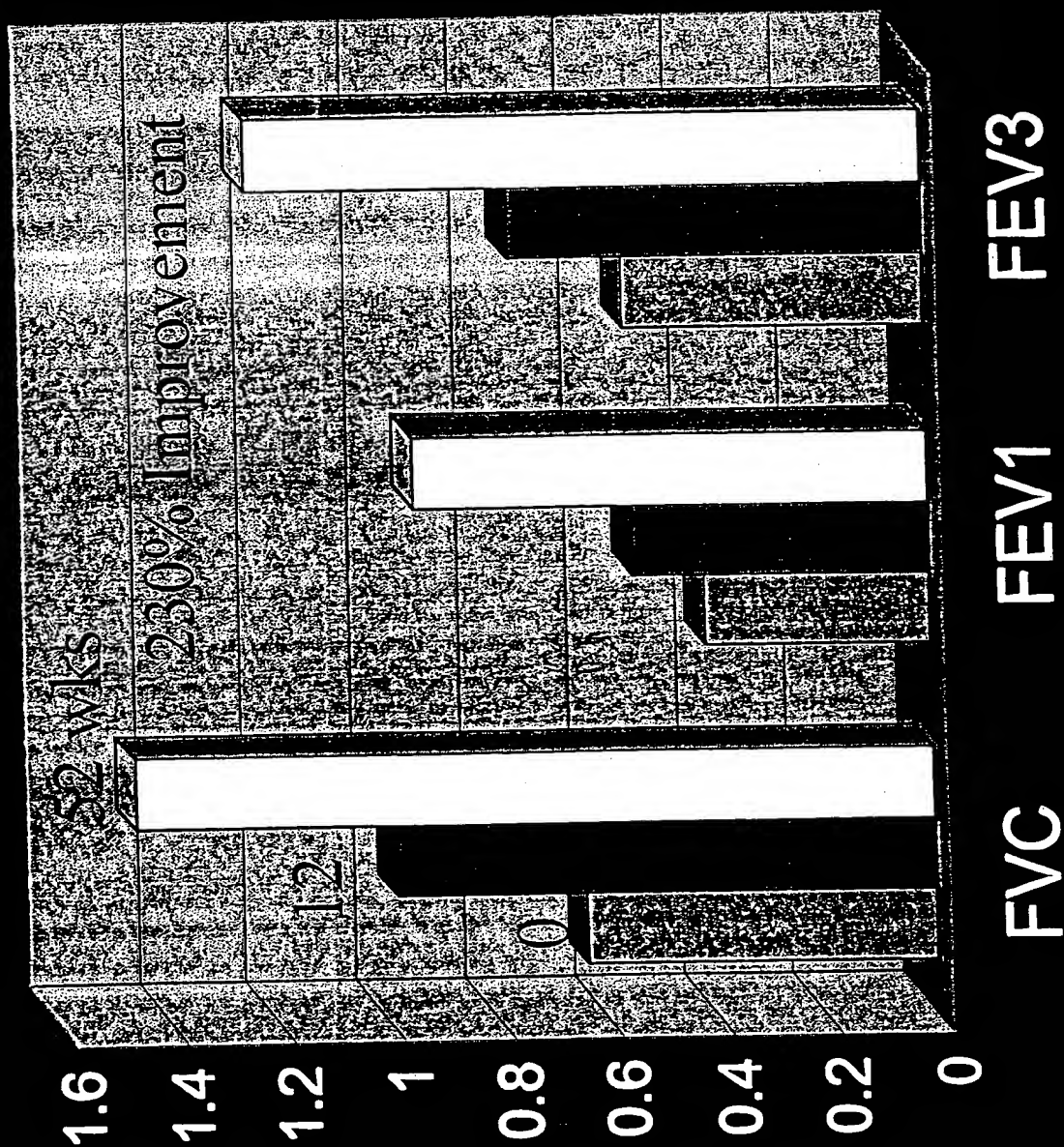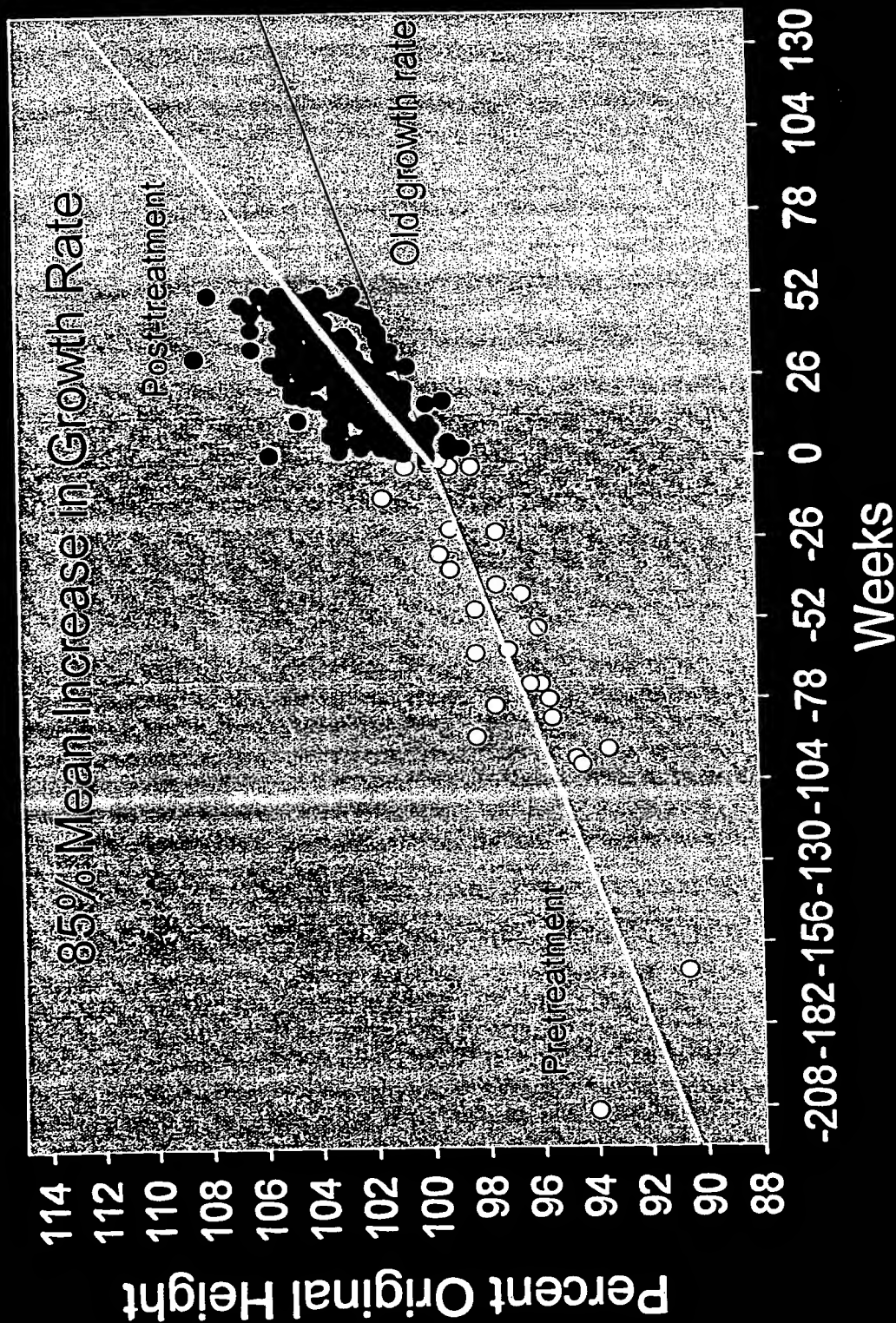
FIGURE 10

FIGURE 11

FIGURE 12.

COMPARISON OF HOST PROTEIN CONTAMINATION BETWEEN A PRIOR AND THE NEW GALLI PROCESS

Chinese Hamster Ovary Host Protein Contamination by ELISA Assay

SOURCE AND BATCH NUMBER	CHOP PROTEIN CONTAMINATION (microgram per milligram)	PERCENT CHOP CONTAMINATION	PURITY OF THE ENZYME FROM CHOP
Prior Process (Carson/REI)			
C9002	14	1.4%	98.6%
C9003	24	2.4%	97.6%
C9004	16	1.6%	98.4%
New Process (Galli)			
P1003	<1.3	<0.13%	>99.9%
P1006	1.2	0.12%	99.9%
P1007	<0.6	<0.06%	>99.9%
P1008	<0.67	<0.067%	>99.9%

FIGURE 12

Comparison of Galli and Carson Material

1 2 3   1   2   3

175--   175--

83--   83--
62--   62--
48--   48--

33--   33--
25--   25--
17--   17--

anit-IDU Western blot   SDS-PAGE silver stain
1:50,000

1 Marker
2 Galli Referenced-0201
3 Carson C9002

5ug/lane

FIGURE 13